Journal of the American College of Cardiology Vol. 60, No. 21, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.07.054

Arterial Wave Reflections and Incident Cardiovascular Events and Heart Failure

MESA (Multiethnic Study of Atherosclerosis)

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Objectives This study sought to assess the relationship between central pressure profiles and cardiovascular events (CVEs) in a large community-based sample.

Background Experimental and physiologic data mechanistically implicate wave reflections in the pathogenesis of left ventricular failure and cardiovascular disease, but their association with these outcomes in the general population is unclear.

Methods Aortic pressure waveforms were derived from a generalized transfer function applied to the radial pressure waveform recorded noninvasively from 5,960 participants in the Multiethnic Study of Atherosclerosis. The central pressure waveform was separated into forward and reflected waves using a physiologic flow waveform. Reflection magnitude (RM = [Reflected/Forward wave amplitude] × 100), augmentation index ([Second/First systolic peak] × 100) and pulse pressure amplification ([Radial/aortic pulse pressure] × 100) were assessed as predictors of CVEs and congestive heart failure (CHF) during a median follow-up of 7.61 years.

Results After adjustment for established risk factors, aortic AIx independently predicted hard CVEs (hazard ratio [HR] per 10% increase: 1.08; 95% confidence interval [CI]: 1.01 to 1.14; $p = 0.016$), whereas PPA independently predicted all CVEs (HR per 10% increase: 0.82; 95% CI: 0.70 to 0.96; $p = 0.012$). RM was independently predictive of all CVEs (HR per 10% increase: 1.34; 95% CI: 1.08 to 1.67; $p = 0.009$) and hard CVEs (HR per 10% increase: 1.46; 95% CI: 1.12 to 1.90; $p = 0.006$) and was strongly predictive of new-onset CHF (HR per 10% increase: 2.69; 95% CI: 1.79 to 4.04; $p < 0.0001$), comparing favorably to other risk factors for CHF as per various measures of model performance, reclassification, and discrimination. In a fully adjusted model, compared to nonhypertensive subjects with low RM, the HRs (95% CI) for hypertensive subjects with low RM, nonhypertensive subjects with high RM, and hypertensive subjects with high RM were 1.81 (0.85 to 3.86), 2.16 (1.07 to 5.01), and 3.98 (1.96 to 8.05), respectively.

Conclusions Arterial wave reflections represent a novel strong risk factor for CHF in the general population. (J Am Coll Cardiol 2012;60:2170–7) © 2012 by the American College of Cardiology Foundation

Several considerations support a mechanistic role for central pressure profiles as causal determinants of cardiovascular disease (1–3). The aortic pressure profile is determined by the interactions between the left ventricle (LV) and the load imposed by the arterial tree (4). Wave reflections arising in peripheral arteries and returning to the proximal aorta during mid to late systole are important determinants of LV afterload. Both animal and human studies have

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Manuscript received March 28, 2012; revised manuscript received July 18, 2012, accepted July 23, 2012.

demonstrated that a loading sequence characterized by prominent late systolic load adversely affects LV structure and function (5–8).

Central pulse pressure and arterial wave reflections can be assessed noninvasively with arterial tonometry. The aortic augmentation index (AIx), which depends on the pressure difference between the first and second systolic peaks (Fig. 1), has been a widely used surrogate of wave reflections. However, AIx is not only influenced by the magnitude of wave reflections but also confounded by their timing, heart rate, body height, and other factors (9,10). When central pressure and flow waveforms are known, the aortic pressure wave can be separated into its forward and reflected components (wave separation analysis), allowing for the measurement of *reflection magnitude* (RM), defined as the dimensionless ratio of the amplitudes of backward/forward waves. This computation does not depend on the calibration of the flow waveform and can be approximated using pressure information only, assuming a triangular or a physiologic flow waveform (Fig. 1) (11,12).

An issue of great interest is whether central pressure parameters are associated with incident cardiovascular events (CVEs) independently of brachial pressures. A recent meta-analysis (3) suggested that central AIx independently predicts CVEs. In contrast, more recent data from 2,232 Framingham Heart Study participants indicated that carotid AIx or pulse pressure did not independently predict major CVEs (13). This study did not perform wave separation analysis and relayed on brachial arterial tonometry for computation of pulse pressure amplification, an approach that has been challenged by some investigators based on anatomic factors that may impede proper applanation tonometry of the brachial artery (14). In another recent study among 1,272 Taiwanese subjects, reflected wave amplitude computed with a triangular flow waveform, but not carotid AIx, predicted all-cause mortality assessed from a National Death Registry 15 years later (15).

Given the adverse impact of wave reflections on the LV (5–7) and the large public health burden of heart failure and cardiovascular disease, further data regarding the association between wave reflections and these outcomes are needed. In this ancillary study of data from the MESA (Multiethnic Study of Atherosclerosis), a large community-based multiethnic cohort study that enrolled adults free of cardiovascular disease (16), this study aimed to assess the relationship between central pressure profiles and: 1) incident hard CVEs; and 2) incident congestive heart failure (CHF).

Abbreviations and Acronyms

AIx = augmentation Index
CHF = congestive heart failure
CVE = cardiovascular event(s)
LV = left ventricle
NRI = net reclassification improvement
PPA = pulse pressure amplification
rIDI = relative integrated discrimination improvement
RM = reflection magnitude

Methods

Study population. MESA enrolled 6,814 men and women ages 45 to 84 years who identified themselves as white, African American, Hispanic, or Chinese and who were free of clinically apparent cardiovascular disease, from 6 U.S. communities between 2000 and 2002 (16). The study was

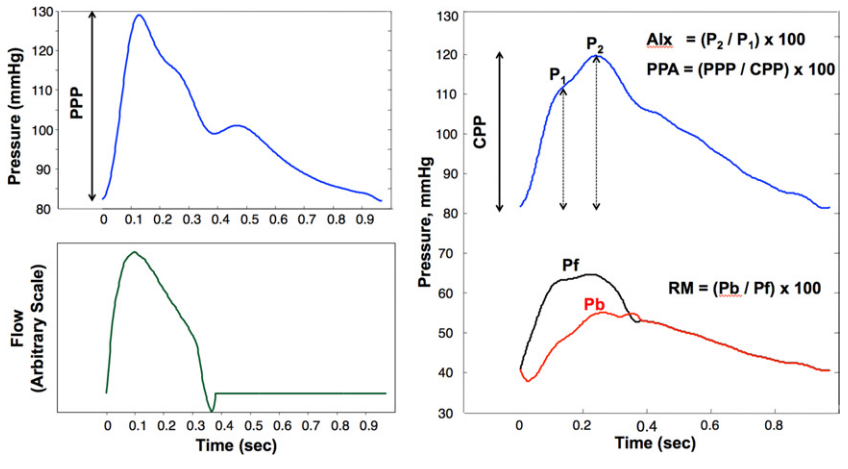


Figure 1 Radial Pressure Waveform

Radial pressure waveform averaged from a 30-s recording **(top left)** and corresponding aortic pressure waveform obtained with a generalized transfer function **(top right)**. Based on identification of the first and second systolic peaks, augmentation index (AIx) can be computed based on the ratio of P2/P1. Pulse pressure amplification (PPA) is computed from the ratio of peripheral (radial) pulse pressure (PPP)/central (aortic) pulse pressure (CPP). Using a physiologic flow waveform **(bottom left),** the aortic wave can be separated into its forward (Pf) and reflected (backward, Pb) waves and reflection magnitude (RM) can be computed based on the ratio of the amplitudes of (Pb/Pf). For consistency, we expressed all indices as percentages (ratios × 100).

approved by the institutional review boards of participating centers and participants gave informed consent.

Data collection. Standardized questionnaires were used to obtain information about cardiovascular risk factors and medication use. Resting blood pressure was measured in triplicate using a Dinamap-Pro100 oscillometric sphygmomanometer (GE Medical Systems, Waukesha, Wisconsin). The average of the last 2 measurements was used. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or antihypertensive medication use (17). Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and glucose were measured after a 12-h fast. *Diabetes mellitus* was defined as fasting glucose ≥126 mg/dl and/or hypoglycemic medication use (18).

Hemodynamic measurements. Radial arterial waveform 30-s recordings were obtained at baseline in the supine position using the HDI/PulseWave-CR2000 tonometry device (Hypertension Diagnostics, Eagan, Minnesota), digitized at 200 Hz and exported for offline processing using custom-designed software written in Matlab (The Mathworks, Natick, Massachusetts).

A generalized transfer function (19) was applied to the radial pressure waveform to obtain a central pressure waveform. Aortic-radial pulse pressure amplification (PPA) was computed as: (radial pulse pressure/aortic pulse pressure) × 100 (Fig. 1). This computation does not depend on calibration of the radial pressure waveform.

The first and second systolic peaks were identified in the aortic pressure waveform as previously described (20). AIx was computed as (Second/First systolic peak) × 100 (Fig. 1). A physiologic flow waveform (11) was used for separation of the pressure wave into forward and reflected waves (21). RM was calculated as shown in Equation 1 (Fig. 1).

$$\frac{\text{backward wave amplitude}}{\text{forward wave amplitude}} \times 100$$

Further details about this analysis methods can be found in the Online Appendix.

Event adjudication. In addition to undergoing 3 on-site examinations, participants were contacted by a telephone interviewer every 9 to 12 months to inquire about incident CVEs. Two physicians independently reviewed copies of medical records and death certificates for hospitalizations and outpatient cardiovascular diagnoses, for blinded endpoint classification using pre-specified criteria (22), as summarized in the Online Appendix. The following endpoints were defined a priori for this study: 1) *hard CVEs,* defined as a composite prevalence of myocardial infarction, resuscitated cardiac arrest, cardiovascular disease–related death, stroke, or stroke-related death; 2) *all CVEs,* defined as a composite prevalence of any hard CVE, angina, other atherosclerosis-related death, or other cardiovascular disease–related death; and 3) CHF, which required clinical symptoms (e.g., dyspnea) or signs (e.g., edema), a physician's diagnosis of CHF, and medical treatment for CHF, in addition to: a) pulmonary edema/congestion by chest radiography; and/or b) dilated ventricle or poor LV function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction. Whereas the 2 former are composite endpoints commonly used in cardiovascular risk studies, CHF was defined as a specific endpoint a priori based on previous experimental data.

Statistical analysis. A more detailed description of the statistical methods can be found in the Online Appendix. The association between hemodynamic measures and time to CVE or CHF was examined using the Kaplan-Meier method and Cox regression. Model goodness-of-fit was assessed with the Akaike's information criterion and Bayesian information criterion (23,24). Model discrimination was assessed with the Harrel's *c*-index (which is analogous to the area under the receiver operator characteristic curve) (23,25). Calibration was assessed with the Hosmer-Lemeshow test. Improvements in subject reclassification was further assessed using the net reclassification improvement (NRI) (23,25), which depends on the increased probability that a new model will categorize case subjects as higher risk and on the decreased probability that it will categorize control subjects as lower-risk, compared to a base model, as explained in more detail in the Online Appendix. We computed 2 versions of the NRI: a category-based NRI based on usual categories for 10-year cardiovascular disease risk (adapted at 5 years as <2.5%, 2.5 to <5%, 5 to <10%, and ≥10%). Because no established categories exist that guide clinical decisions for CHF risk, we computed category-free reclassification measures, which are independent on arbitrarily defined risk thresholds (26). These include the category-free NRI and the relative integrated discrimination improvement (rIDI), which expresses the relative improvement in discrimination slopes (difference in mean predicted probabilities between case and control participants) between the base model and new model (23,25–27). Various indices of model performance were used to: 1) assess the added predictive value of central pressure indices; and 2) compare the predictive value of aortic hemodynamic indices to that of well-established risk factors, as previously described (23).

All tests were 2-sided with alpha = 0.05. Analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, Illinois).

Results

Of 6,336 participants who underwent radial tonometry, 6,153 (97.1%) had technically adequate data. Central waveforms from 164 subjects had no discernible inflections (due to merging of the first and second peaks) or >1 inflection, impeding adequate identification of the first and second systolic peaks. Twenty-nine participants had no follow-up

Table 1 Baseline Characteristics of Study Participants (N = 5,960)

Age, yrs	62 (53–70)
Sex	
Male	2,862 (48)
Female	3,096 (52)
Ethnicity	
White	2,240 (37.6)
African American	1,620 (27.2)
Chinese American	728 (12.2)
Hispanic American	1,370 (23.0)
Body measurements	
Height, cm	166 (159–174)
Weight, kg	77.1 (66.2–89.4)
BMI, kg/m^2	27.5 (24.6–31.2)
Hemodynamic variables	
Brachial SBP, mm Hg	124 (111–140)
Brachial DBP, mm Hg	72 (65–78.5)
Heart rate, bpm	63 (57–70)
Aortic augmentation index, %	145 (135–159)
RM, %	84 (81–87)
PPA, %	1.10 (1.05–1.17)
Laboratory analysis, mg/dl	
Total cholesterol	192 (171–215)
LDL-cholesterol	116 (96–136)
HDL-cholesterol	48 (40–59)
Triglycerides	112 (78–162)
Estimated GFR, ml·min^{-1}·1.73 m^{-2}	80 (70–92)
Risk factors	
Diabetes mellitus	755 (12.7)
Current smoking	2,151 (36.1)
Hypertension	2,667 (44.8)
Hypertension medication use	2,207 (37)
CVEs	
Myocardial infarction	112 (1.9)
Heart failure	104 (1.7)
Stroke	100 (1.7)
All hard CVEs	148 (2.5)
All CVEs	258 (4.3)
Any hard CVE	241 (4.0)
Any CVE	356 (6.0)

Values are median (interquartile range) or n (%).

BMI = body mass index; CVE = cardiovascular event(s); DBP = diastolic blood pressure; GFR = glomerular filtration rate; IQR = interquartile range; RM = reflection magnitude; SBP = systolic blood pressure.

information, leaving 5,960 participants in the analysis. Table 1 shows baseline characteristics of subjects included in this study.

Cardiovascular events. During a median follow-up of 7.61 (interquartile range: 7.34 to 7.78) years, 407 subjects experienced a first CVE, 281 subjects experienced a first hard CVE, and 117 experienced a first episode of CHF. Hazard ratios (HRs) for incident CVE and CHF associated with a 10-point increase in AIx, RM, or PPA are shown in Table 2. Table 2 also shows standardized HRs (those associated with a 1-SD increase in the predictors). In adjusted analyses, AIx was independently associated with hard CVEs (model 3, Table 2) (HR per 10% increase: 1.08; 95% confidence interval [CI]: 1.01 to 1.14; p = 0.016). The category-free NRI, rIDI and increase in *c*-index achieved by adding PPA to the other variables in this model were 0.036, 0.002, and 0.004, respectively. PPA was independently associated with all CVEs (model 3, Table 2) (HR per 10% increase: 0.82; 95% CI: 0.70 to 0.96; p = 0.012). The category-free NRI, rIDI, and increase in *c*-index achieved by adding PPA to the other variables in this model were 0.10, 0.02, and 0.002, respectively. PPA and AIx were not independently associated with incident CHF.

RM was independently associated with incident CVEs. After adjustment for age, sex, ethnicity, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, height, weight, diabetes mellitus, total cholesterol, HDL cholesterol, current smoking, heart rate, and glomerular filtration rate, a 10% increase in RM was predictive of a higher risk for CVEs (HR: 1.34; 95% CI: 1.08 to 1.67; p = 0.009) and hard CVEs (HR per 10% increase: 1.46; 95% CI: 1.12 to 1.90; p = 0.006). The category-free NRI, rIDI, and increase in *c*-index for the prediction of all CVEs achieved by adding RM to the other variables shown in model 3 (Table 2) were 0.15, 0.05, and 0.002, respectively. The category-free NRI, rIDI, and increase in *c*-index for the prediction of hard CVEs when RM was added to the other variables shown in model 3 (Table 2) were 0.13, 0.08, and 0.002, respectively.

RM was strongly predictive of incident CHF (HR per 10% increase: 2.69; 95% CI: 1.79 to 4.04; p < 0.0001; Table 2). Table 3 shows independent predictors of incident CHF in a fully adjusted model, together with standardized HRs for each term, in order to allow for easier comparison between various predictors. The full model is similar to the one used in Table 2, with the exceptions of height and weight, which were replaced by body mass index to more intuitively assess the independent contribution of obesity to CHF risk prediction in the model. Table 3 also shows improvements in model performance observed when individual predictors were added to a model containing all other variables except the predictor in question. RM was associated with a standardized HR of 1.61 (95% CI: 1.32 to 1.96), the largest Wald statistic and the greatest decreases in Akaike's information criterion and Bayesian information criterion (indicating improvement in model fit) and the greatest increases in IDI and rIDI. With the exception of age, a nonmodifiable risk factor, RM was associated with the greatest NRI. Of note, these improvements in model performance were also superior to changes induced by adding systolic blood pressure and diastolic blood pressure together.

The addition of RM to a model containing all other variables shown in Table 3 resulted in a category-free NRI of 0.38 and a rIDI of 0.48, indicating a 48% relative increase in the discrimination slope achieved by all variables in the base model. The addition of RM to the model resulted in a category-based NRI of 0.17. A category-dependent reclassification table can be found in Online Table 1. The full

Table 2 Results of Cox Proportional Hazards Models Examining the Relationship Between Hemodynamic Variables at Baseline and the Risk for CVEs, Including Heart Failure, During Follow-Up*

	Crude (N = 5,960)			Adjusted Model 1† (n = 5,937)			Adjusted Model 2† (n = 5,934)		
Hemodynamic Variable	HR (95% CI) per 10% Increase	Standardized HR (95% CI)	p Value	HR (95% CI) per 10% Increase	Standardized HR (95% CI)	p Value	HR (95% CI) per 10% Increase	Standardized HR (95% CI)	p Value
RM‡									
All CVEs	1.48 (1.2–1.81)	1.21 (1.09–1.34)	<0.0001	1.38 (1.11–1.71)	1.17 (1.05–1.30)	0.004	1.34 (1.08–1.67)	1.15 (1.04–1.28)	0.009
All hard CVEs	1.66 (1.29–2.13)	1.28 (1.13–1.45)	<0.0001	1.52 (1.17–1.98)	1.23 (1.08–1.40)	0.002	1.46 (1.12–1.90)	1.20 (1.06–1.37)	0.006
Heart failure	2.61 (1.75–3.88)	1.60 (1.32–1.94)	<0.0001	2.75 (1.83–4.12)	1.64 (1.35–2.00)	<0.0001	2.69 (1.79–4.04)	1.62 (1.33–1.98)	<0.0001
Augmentation index§									
All CVEs	1.05 (1.004–1.09)	1.11 (1.01–1.21)	0.031	1.03 (0.99–1.08)	1.07 (0.98–1.19)	0.19	1.05 (1.00–1.11)	1.12 (1.00–1.25)	0.052
All hard CVEs	1.07 (1.02–1.13)	1.17 (1.05–1.30)	0.005	1.05 (0.99–1.11)	1.12 (0.99–1.26)	0.058	1.08 (1.01–1.14)	1.17 (1.03–1.33)	0.016
Heart failure	1.06 (0.98–1.14)	1.14 (0.97–1.34)	0.14	1.03 (0.95–1.12)	1.07 (0.89–1.28)	0.50	1.08 (0.99–1.17)	1.17 (0.97–1.42)	0.11
PPA‖									
All CVEs	0.92 (0.82–1.02)	0.92 (0.83–1.02)	0.09	0.98 (0.88–1.10)	0.99 (0.89–1.10)	0.78	0.82 (0.70–0.96)	0.82 (0.71–0.96)	0.012
All hard CVEs	0.92 (0.81–1.04)	0.92 (0.81–1.04)	0.19	1.02 (0.89–1.16)	1.02 (0.90–1.15)	0.81	0.87 (0.72–1.05)	0.87 (0.73–1.05)	0.15
Heart failure	0.91 (0.75–1.11)	0.92 (0.76–1.11)	0.37	1.05 (0.86–1.28)	1.04 (0.86–1.27)	0.67	0.82 (0.61–1.10)	0.82 (0.62–1.09)	0.18

*Hazard ratios correspond to a 10% increase (or a 10-point increase in the indices shown between parentheses in the formulas above). Standardized HRs represent the risk increase for an increase in 1 standard deviation of the examined variable. †Adjusted model 1 includes age, gender, total cholesterol, HDL-cholesterol, smoking, systolic and diastolic blood pressure, diabetes mellitus. Adjusted model 2 further adjusts for ethnicity, body height, body weight, antihypertensive medication use, heart rate, and estimated glomerular filtration rate. Complete covariate data was available from 5,934 subjects. ‡RM = (Reflected wave amplitude/Forward wave amplitude) × 100. §Augmentation index = (Second systolic peak/First systolic peak) × 100. ‖PPA = (Radial pulse pressure/Aortic pulse pressure) × 100.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

model containing RM demonstrated adequate calibration (Hosmer-Lemeshow chi square: 8.50; p = 0.49).

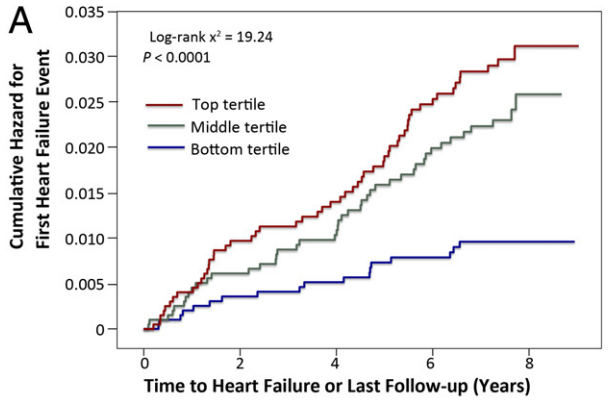
Finally, in order to more directly compare the value of brachial pulse pressure versus RM as predictors of CHF, RM or brachial pulse was separately added to a base model that included age, sex, body mass index, diabetes mellitus, ethnicity, antihypertensive medication use, total cholesterol, HDL cholesterol, current smoking, heart rate, and estimated glomerular filtration rate. When RM was added to this base model, the standardized HR for RM was 1.54 (95% CI: 1.26 to 1.88; p < 0.0001), with an achieved NRI, rIDI, and increase in *c*-index of 0.32, 0.42, and 0.011, respectively. When pulse pressure was added to this base model, the standardized HR for RM was 1.42 (95% CI: 1.18 to 1.70; p < 0.0001), with an achieved NRI, rIDI and increase in *c*-index of 0.27, 0.20, and 0.011, respectively.

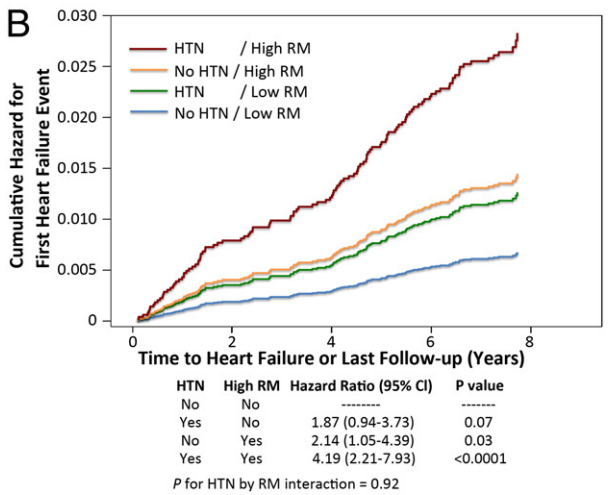
Figure 2A shows cumulative hazard curves for incident CHF among subjects, stratified by RM tertiles. There was a progressive increase in CHF risk with increasing RM tertile (p < 0.0001). For further comparison of the risk for CHF associated with hypertension versus increased RM, the population was stratified according to the presence (prevalence: 45%) or absence of hypertension. The population was also stratified into those above or below the 55th RM percentile to obtain a prevalence of "high" RM identical to the prevalence of hypertension (45%), allowing for a more direct comparison of the contribution of each factor to CHF risk in the population. Figures 2B and 2C show adjusted cumulative hazard functions for each substratum according to the presence or absence of hypertension and high RM. As shown, nonhypertensive subjects with low RM were at lowest risk, hypertensive subjects with high RM were at highest risk, and hypertensive subjects with low RM and

Table 3 Predictors of Incident Heart Failure in Multivariate Analysis (N = 5,934)*

	Full Model With Adjusted HRs (*c*-Index: 0.802; AIC: 1893; BIC: 1943)			Effects of Adding Individual Predictors to a Model Containing All Other Variables					
Predictor	Standardized HR (95% CI)	Wald Statistic	p Value	Change in BIC†	Change in AIC†	Change in *c*-Index‡	NRI‡	IDI‡	rIDI‡
Age (10 yrs)	1.62 (1.26–2.08)	14.44	<0.0001	−10.10	−12.87	0.020	0.47§	0.010§	0.22§
Male	1.74 (1.38–2.21)	21.37	<0.0001	−17.09	−19.85	0.015	0.34§	0.017§	0.44§
BMI (10 kg/m^2)	1.26 (1.03–1.55)	4.83	0.028	0.15	−2.62	0.007	0.32§	0.002	0.050
Diabetes mellitus	1.24 (1.07–1.44)	8.37	0.004	−3.09	−5.86	0.010	0.019	0.003	0.061
SBP (10 mm Hg)	1.69 (1.33–2.13)	18.97	<0.0001	−13.10	−15.86	0.013	0.31§	0.011§	0.25§
DBP (10 mm Hg)	0.67 (0.52–0.86)	9.71	0.002	−4.94	−7.70	0.006	0.15§	0.007§	0.14§
Reflection magnitude (10%)	1.61 (1.32–1.96)	22.03	<0.0001	−17.79	−20.55	0.011	0.38§	0.018§	0.48§
SBP and DBP together‖	—	—	—	−8.46	−13.98	0.013	0.28§	0.011§	0.25§

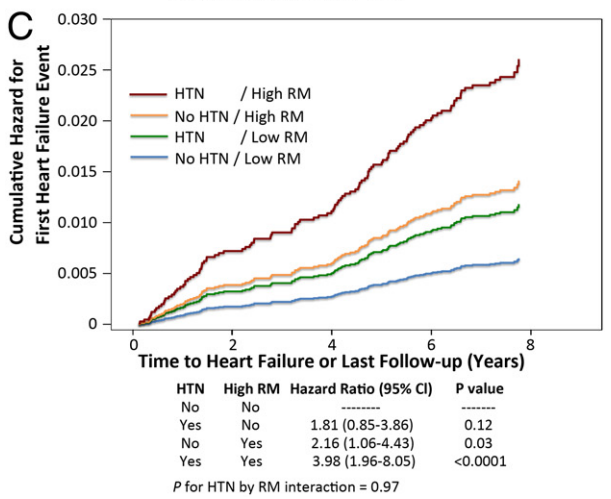
*Only significant predictors of CHF are shown. However, all models are also adjusted for ethnicity, antihypertensive medication use, total cholesterol, HDL-cholesterol, current smoking, heart rate, and estimated GFR. All HRs are standardized. †Larger decreases (changes with negative sign) indicate a larger improvement in model fit. ‡Larger increases indicate a larger improvement in performance in reclassification or discrimination. §p < 0.05. ‖Improvements in model performance when both SBP and DBP are added to a model containing all other variables contained in the full model.
AIC = Akaike information criterion; BIC = Bayesian information criterion; IDI = integrated discrimination improvement; rIDI = relative integrated discrimination improvement; NRI = net reclassification improvement (category free); other abbreviations as in Tables 1 and 2.





HTN	High RM	Hazard Ratio (95% CI)	P value
No	No	--------	-------
Yes	No	1.87 (0.94-3.73)	0.07
No	Yes	2.14 (1.05-4.39)	0.03
Yes	Yes	4.19 (2.21-7.93)	<0.0001

P for HTN by RM interaction = 0.92



HTN	High RM	Hazard Ratio (95% CI)	P value
No	No	--------	-------
Yes	No	1.81 (0.85-3.86)	0.12
No	Yes	2.16 (1.06-4.43)	0.03
Yes	Yes	3.98 (1.96-8.05)	<0.0001

P for HTN by RM interaction = 0.97

Figure 2 **Reflection Magnitude as a Predictor of Incident Heart Failure**

(A) Cumulative hazard for heart failure among subjects stratified according to tertiles of reflection magnitude (RM). **(B)** Hazard function for incident of heart failure in subjects stratified according to the presence or absence of hypertension (prevalence: 45%) or reflection magnitude above ("high" RM) or below ("low" RM) the 55th percentile (prevalence of "high" RM: 45%), adjusted for other significant heart failure predictors shown in Table 3. **(C)** Analogous hazard functions after further adjustment for ethnicity, antihypertensive medication use, total-cholesterol, HDL-cholesterol, current smoking, glomerular filtration rate, and heart rate.

nonhypertensive subjects with high RM were at intermediate risk for incident CHF.

Discussion

This study identifies an important novel independent risk factor for new-onset CHF among adults in the general population who are free of clinically apparent cardiovascular disease. In this large multiethnic sample, the magnitude of arterial wave reflections assessed noninvasively via radial arterial tonometry was a strong predictor of incident CHF. RM was also a significant predictor of incident CVE, but its association with this composite endpoint was not as strong as its association with CHF.

Physiologic principles (28) and experimental studies (4–6) directly implicate wave reflections in the pathogenesis of LV failure, but this is the first study to assess their association with the risk for incident CHF in humans. The pressure (and flow) wave generated by the LV (forward wave) is transmitted by conduit vessels and partially reflected at sites of impedance mismatch, such as points of branching or change in wall diameter or material properties along the arterial tree as well as at the junction of small conduit arteries with high-resistance arterioles, in which mean pressure falls precipitously (4,29). Multiple small reflections travel back to the proximal aorta and merge into a "net" reflected wave. It has been long known that arterial wave reflections profoundly affect LV afterload (4,28–30). Due to the finite wave transit time from the heart to reflection sites and back to the proximal aorta, in adults beyond youth, wave reflections typically increase LV afterload in mid to late systole (4,29). For any given level of systolic blood pressure, a pattern characterized by prominent late-systolic load has been unequivocally demonstrated to exert deleterious effects on LV structure and function in animal models (4–6), observations that have been supported by human studies (7,8). Consistent with these mechanistic data, this study indicates that wave reflections are important predictors of CHF risk. Wave reflections are thought to be generated predominantly near muscular (medium-sized) and smaller arterial segments and are highly modifiable. Vasoactive drugs such as organic nitrates profoundly decrease wave reflections despite small effects on brachial pressures (31). Therefore, these findings not only have implications for CHF risk assessment but also may identify a potential novel therapeutic target for CHF prevention. However, this study does not prove that this is a suitable therapeutic strategy, and this issue will need to be addressed in appropriately designed clinical trials.

Some previous studies assessing the association between central pressures and incident CVE included populations with manifest cardiovascular or renal disease (3). Studies in the general population (e.g., the Strong Heart Study [32] or Framingham Heart Study [13]) have been restricted to a single ethnic group and examined composite CVE endpoints. Furthermore, previous studies assessed central pulse

pressure and AIx, rather than RM assessed with wave separation analysis. Several studies suggest that AIx is predictive of composite CVE endpoints among subjects with established cardiac or renal disease (3). However, central AIx and pulse pressure did not predict CVE independently of brachial pressures among 2,232 participants enrolled in the Framingham Heart Study. In this study, the adjusted relationship between AIx/PPA and incident CVE was not consistent. Although AIx was an independent predictor of hard CVEs, whereas PPA was an independent predictor of all CVEs in multivariate analyses, knowledge of these variables yielded negligible increases in reclassification and discrimination for these endpoints. Unlike RM, PPA/AIx were not predictive of incident CHF. We emphasize that these findings do not indicate that central pulse pressure is irrelevant for cardiovascular risk, but rather indicate that, when considering the broad distribution of brachial pressures within a population, knowledge of the smaller difference between peripheral and central pulse pressure (PPA) does not provide substantial incremental risk prediction for hard CVEs/CHF.

The different predictive performance of AIx compared to RM has several potential explanations. AIx is not only influenced by RM but also strongly dependent on reflection timing, heart rate, body height, and hemodynamic phenomena unrelated to wave reflections (4,9,10,33). Computation of AIx is dependent on the accuracy of high-frequency components of measured pressure (which produce sharp inflections in the waveform), which may be less accurately reproduced with a generalized transfer function due to their higher interindividual variability (34). In contrast, RM is less sensitive to confounding factors listed above and its computation depends predominantly on low-frequency pressure harmonics, which relate more consistently between the aortic and radial sites among different individuals (34) and may therefore be better reproduced with a generalized transfer function.

This study is the largest to date to assess the association between central pressure profiles and incident CVE. Other strengths of this investigation include the multiethnic community-based sample, standardized assessments, and careful event adjudication using hard criteria for CHF/CVE. However, it is important to acknowledge some limitations. This observational study cannot prove a causal link between wave reflections and CHF/CVE. Central flow was not measured; a physiologic flow waveform was assumed, an imperfect approach that, although better related to incident CHF/CVE than AIx, provides only an approximation of true RM. This raises the possibility that the predictive ability of RM may be improved if more accurately measured with subject-specific flow waveform data. Because participants had no known cardiovascular disease at baseline, this cohort represents a particularly healthy sample of the general population, which is, however, ideal for examining early vascular changes predisposing to CHF. As a consequence, the absolute risk of CHF in this cohort was relatively low and the observed number of events was insufficient for gender-specific subanalyses, which, however, should be feasible in the future as more events accumulate in the cohort. Despite this large, multiethnic sample, it would be desirable to replicate the findings in other populations to better establish their generalizability. Finally, aortic pulse wave velocity, an index of aortic wall stiffness, which also impacts LV afterload, was not measured. However, aortic pulse wave velocity affects predominantly the timing (rather than the magnitude) of wave reflections, and the LV senses only operating load and not large arterial material properties per se. It is possible that aortic pulse wave velocity and RM provide complementary information about cardiovascular risk. This should be addressed in future studies.

Conclusions

In an ethnically diverse population free of cardiovascular disease at baseline, RM was independently associated with incident CVE and strongly associated with incident CHF. Arterial wave reflections represent an important novel risk factor for CHF and a potential therapeutic target for primary CHF prevention.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of MESA for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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Key Words: arterial hemodynamics ■ cardiovascular risk ■ heart failure ■ left ventricular afterload ■ wave reflections.

APPENDIX

For a detailed Methods section, please see the online version of this article.